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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,989	COLLIER ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *1-4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/4/06, 3/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 5-7 and the species of SEQ ID NO: 1 and 2 in the reply filed on October 28, 2008 is acknowledged. The traversal is on the ground(s) that claims 1, 4 and 7 have been amended to clarify that the variant allele (A11C) of the ADRB2 gene is correlated with milk production. It is asserted that the cited prior art of Roets does not teach or enable the skilled artisan to determine which bulls posses an A11C allele in the ADRB2 gene that will produce cows with desired milking traits. Applicants conclude that Roets cannot be relied upon to establish a lack of unity of invention. This is not found persuasive because A 371 application is considered to have unity of invention only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression "special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the instant application, the linking technical feature of claims 5 and 6 of kits comprising primer pairs which flank the 11th nucleotide of the ADRB2 gene and a restriction enzyme specific for the CCCGGG site was obvious at the time the invention was made, as set forth in detail below. Further, note that unity of invention is considered only with respect to the independent claims in an international application, and not with respect to the dependent claims. Accordingly, there is no special technical feature linking each of the claimed inventions.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-7 are pending.

Claims 5-7 have been examined herein. Claim 7 has been examined to the extent that the claim reads on the elected combination of primers of SEQ ID NO: 1 and 2. The primers of SEQ ID NO: 3 and 4 are withdrawn from consideration as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 28, 2008.

3. The examiner reviewing your application at the PTO has changed. To aid in correlating papers in this application, all further correspondence regarding this application should be directed to examiner Carla Myers.

Priority

4. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, a petition

under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. However, Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

In particular, an ADS listing the documents to which priority is claimed should be provided or the first line of the specification should be amended to recite, for example: This application is the National Stage of International Application PCT/US04/30774, filed September 21, 2004, which claims the benefit of U.S. Provisional Application 60/505,113, filed September 23, 2003. Note that the claim to priority to the provisional application filed on September 23, 2003 was originally set forth in the transmittal papers filed March 23, 2006.

Claim Rejections - 35 USC § 112 – Written Description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

In analyzing claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note that with regard to

genus/species situations, a "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed."

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. To ascertain whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. It is then determined whether a representative number of species have been defined by other identifying characteristics.

In the present situation, the claims are drawn to kits comprising a pair of primers which flank the 11th nucleotide position of the bovine beta2-adrenoreceptor (B2AR/ADRB2) coding sequence inclusive of the start codon ATG, wherein the primers enable detection of a SNP at said 11th nucleotide position.

The primers are not defined in terms of any structural properties. For example, the primers are not defined in terms of their nucleotide sequence or their length. The primers are not defined in terms of the sequence to which they hybridize or their specificity of hybridization (e.g., the conditions under which they hybridize to a particular target nucleotide sequence). Nor are the primers defined in terms of the distance from

the 11th nucleotide of the B2AR gene to which they may hybridize. Thereby, the claims include primers of any nucleotide sequence and of any length which hybridize at any distance upstream and/or downstream of the 11th nucleotide of the B2AR gene. The primers may consist of sequences or may hybridize to sequences in 5' or 3' untranslated regions, in genes that are adjacent to the B2AR gene in a bovine or non-bovine chromosome, or genes that are at a substantial distance to the B2AR gene. Note that the claims do not set forth how the primers "enable detection of a single nucleotide polymorphism at the 11th nucleotide position." Thereby, the primers may be useful in mapping studies, in long sequencing methods, or in assays that detect a SNP in linkage disequilibrium with the A11C SNP. While the primers hybridize to the above noted regions, they need not consist of a fragment of these regions. But rather may share limited sequence identity and still retain the ability to "flank" and thereby hybridize to the 11th nucleotide position of the B2AR gene.

Accordingly, the claims encompass a significantly large genus of primers not defined in terms of any structural features, wherein the genus of primers may include nucleotide sequence fragments that are allelic variants, splice variants, or homologues of the bovine B2AR gene, of the B2AR gene of non-bovine organisms, and of any gene sequences 5' or 3' to the B2AR gene in bovine and non-bovine organisms.

However, the specification exemplifies 2 particular primer pairs that amplify the nucleotide sequence of the bovine B2AR gene in which the A11C mutation, encoding for a Pro4His substitution, is present – namely the primer pair of SEQ ID NO: 1 and 2, and the primer pair of SEQ ID NO: 3 and 4 (see page 8 of the specification). The

specification (page 2) also teaches that the DNA sequences of the 1257 bp ADRB2 gene coding region, a 5' untranslated region of 223 bases upstream of the ATG start site and a 3' region 550 bases downstream from the TAA stop codon were known available in public databases at the time the invention was made.

Accordingly, the specification has described in terms of its complete structure only 2 primer pairs – i.e., SEQ ID NO: 1 and 2, and SEQ ID NO: 3 and 4. Further, the prior art has disclosed a sequence of a total of 2030 nucleotides from which fragments can be obtained to generate primers that hybridize to the region flanking the 11th nucleotide of the bovine B2AR gene.

No additional members of the claimed genus have been sufficiently described in terms of any other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.).

Note that the prior art of Einspanier et al (Endocrinology. 1999. 140: 2679-2684) exemplifies primer pair that hybridize to bovine B2AR gene sequences, although in combination the primer pair does not amplify the B2AR sequence that includes the 11th nucleotide of the coding region (see page 2680, col. 1). Further, Hughes et al (Biochimica et Biophysica Acta. 1997. 1356: 281-291) teaches primer pairs that consist of nucleotide sequences of the mouse B2AR gene (page 284). However, the present specification does not contemplate the particular primer pairs of Einspanier or Hughes. Accordingly, the specification cannot be relied upon for providing support for the particular primer pairs of Einspanier or Hughes.

Thus, applicant has established possession of only a limited number of particular primers in a genus which comprises millions of different possibilities of primers comprising fragments that consist of or share some unspecified level of sequence identity or complementarity with bovine or non-bovine sequences present on the chromosome carrying the B2AR gene.

In the absence of a representative number of species of the claimed genus, there is insufficient descriptive support for the currently claimed genus of any pair of primer primers that flank the 11th nucleotide position of the bovine B2AR gene.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of the current claims comprises the use of primer pairs which the present inventors were not in the possession of, or which were not known to the inventors.

This finding is also emphasized in *Ex Parte Kubin* (No. 2007-0819, Bd. Pat. App. & Int. May 31, 2007), wherein it is stated that :

"Although there is often significant overlap" between the enablement and written description requirements, "they are nonetheless independent of each other." University of Rochester, 358 F.3d at 921, 69 USPQ2d at 1891. An "invention may be enabled even though it has not been described." Id. Such is the situation here. While we conclude one skilled in the art would have been able to make and use the full scope of claim 73 through routine experimentation, we find Appellants did not describe the invention of claim 73 sufficiently to show they had possession of the claimed genus of nucleic acids. See, e.g., Noelle v. Lederman, 355 F.3d 1343, 1348, 69 USPQ2d 1508, 1513 (Fed. Cir. 2004) ("invention is, for purposes of the 'written description' inquiry, whatever is now claimed").

Further, "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895." Thereby, a showing of how to potentially identify and make other primer pairs that directly or indirectly detect the SNP at position 11 of the B2AR gene is not sufficient to establish that Applicant's were in possession of the invention as broadly claimed.

As noted in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), the Federal Circuit concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Accordingly, the claims fail to meet the written description requirement because the claims encompass a significantly large genus of primer pairs which are not described in the specification.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al (Biochimica et Biophysica Acta. 1997. 1356: 281-291) in view of Ahern (The Scientist. July 1995. 9(15): 20-25), as evidenced by Einspanier et al (Endocrinology. 1999. 140: 2679-2684).

Claims 5 and 6 are drawn to kits comprising a restriction enzyme that recognizes the CCCGGG sequence, and particularly the restriction enzyme SmaI, and a pair of

primers which flank the 11th nucleotide position of the bovine beta2-adrenoreceptor (B2AR/ADRB2) coding sequence inclusive of the start codon ATG, wherein the primers enable detection of a SNP at said 11th nucleotide position. It is noted that the primers are not defined in terms of any structural properties and that the specification does not define the term "flank". Accordingly, the claims are considered to be inclusive of kits comprising pairs of one type of primer or pairs of different types of primers that hybridize to some degree to nucleotides 5' or 3' of the 11th nucleotide of the bovine B2AR gene.

Hughes teaches methods for amplifying B2AR nucleic acid sequences and for cloning B2AR nucleic acid sequences into pBluescript II SK + vector (page 284). Hughes exemplifies a number of primers that hybridize to upstream and coding sequences of the mouse B2AR gene. In particular, Hughes teaches the primer "1R" that consists of CAGAACTCGCACCAGAAGTT that shares significant sequence identity with (and thereby hybridizes to the inverse complement of nucleotides 530 to 546 of the B2AR gene.

```
Query  4    AACTCGCACCAGAAGTT  20
            ||||| ||||||||||
Sbjct  546  AACTCACACCAGAAGTT  530
```

Note that the numbering of the bovine B2AR gene is relative to that set forth in the reference of Einspanier et al (Figure 4), and that the 11th nucleotide of the coding sequence of the B2AR gene occurs at nucleotide position 234 in the sequence of Einspanier. Note also that the Einspanier reference is cited to establish what is a property of the primers and the positions that they hybridize to within the bovine B2AR gene.

Hughes also teaches the primer "1F" which consists of GGTGCGCTCACCTGCTAACCTGC and which shares significant sequence identity to (and thereby hybridizes to) nucleotides197 to 210.

```
Query  2    GTGCGCTCACCTGCTAACCTGC 23
            ||||||||||||| | |||||
Sbjct  197  GTGCGCTCACCTGCCAGCCTGC 218
```

Thereby, primers "1F" and "1R" alone (as multiple copies) or in combination constitute pairs of primers that hybridize to and flank the 11th nucleotide of the coding region of the bovine B2AR gene, and which have the property that they could be used to detect a polymorphism at position 11 of the coding region of the bovine B2AR gene.

Further, Hughes (page 284) teaches cloning B2AR sequences into a pBluescript II SK + vector with the 5' end being cloned into the SmaI site of the vector. It is clear from the teachings of Hughes, that cloning of the B2AR sequences into the Bluescript vector would require digestion with the restriction enzyme SmaI in order to permit insertion at the SmaI site. It is noted that it is a property of the SmaI restriction enzyme that it specifically recognizes and cleaves the CCCGGG site.

Accordingly, the method of Hughes requires the use of primer pairs that hybridize to nucleic acid sequences that flank the 11th position of the bovine B2AR gene and the SmaI restriction enzyme that is specific for the CCCGGG site.

Hughes does not teach packaging the B2AR primer pairs and SmaI restriction enzyme in a kit.

However, reagent kits for performing DNA analysis methods were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern

discloses the general concept of kits for performing detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) teaches that kits also provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primer pairs and SmaI restriction enzyme of Hughes in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify and clone B2AR nucleic acid sequences, in order to permit further characterization and analysis of the B2AR nucleic acid sequences.

7. Claims 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al in view of Ahern, and further in view of Einspanier et al (Endocrinology. 1999. 140: 2679-2684), Hogan (US Pat. 5,541,308, July 30, 1996), and Buck et al. (Biotechniques, 1999, 27:528-536.

The teachings of Hughes and Ahern are presented above. In combination, Hughes and Ahern teach a kit comprising primer pairs that flank the 11th nucleotide of the coding region of the bovine B2AR gene and the restriction enzyme SmaI, which recognizes the CCCGGG restriction enzyme site.

Hughes does not teach a primer pair which consist of the bovine nucleotide sequence of SEQ ID NO: 1 and 2.

However, Hughes does exemplify a number of primers for amplifying B2AR nucleic acid sequences and teaches selecting primers that hybridize to both 5' non – coding sequences and primers that hybridize to coding sequences.

Further, Einspanier (Figure 4) teaches the complete sequence of the bovine B2AR gene, including the full coding region, and 5' and 3' non-coding sequences. Einspanier also teaches methods for amplifying and detecting bovine B2AR mRNAs present in bovine oviduct (page 2680). The amplification reactions were performed using primers that hybridize to and amplify bovine B2AR coding sequences. Einspanier also teaches sequencing clones comprising the bovine B2AR gene sequences and the B2AR amplified sequences (page 2860, col. 1). The authors also discuss the important functional properties of the bovine B2AR gene and protein in bovine oviduct (page 2684).

Extensive guidance is provided in the prior art as to how to make and use primers that detect multiple variants of a virus, or which are specific for one variant of a virus. Designing primers which are equivalents to those taught in the art requires only routine experimentation. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design additional primers to amplify the full length sequence and portions of the sequence of the bovine B2AR gene. .

For example, Hogan (col. 6, line 65 to col. 7, line 29) provides extensive guidance for the selection of oligonucleotide primers and probes,

> "Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{o}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (column 10, lines 13-15).

Further, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected

by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Given that the prior art teaches the sequences of bovine B2AR coding region and the 5' and 3' untranslated regions, and provides the motivation to obtain additional primers and probes to amplify and detect and clone bovine B2AR gene sequences, and provides extensive guidance as to how to select additional primers the bovine B2AR gene sequences, it would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made to have generated additional primers, including the particular primer pair of present SEQ ID NO: 1 and 2.

Hughes and Einspanier both teach selecting primer pairs that amplify portions of or the complete sequence of the B2AR gene. Einspanier provides the motivation to specifically amplify and detect bovine B2AR gene sequences, and thereby to generate primer pairs to the bovine B2AR gene, in order to study the expression and activity of

bovine B2AR in oviduct tissue. Thereby, the combined prior art provides both the motivation and a reasonable expectation of success of obtaining additional bovine B2AR primers, including the primers of SEQ ID NO: 1 and 2. Note that no unexpected results have been established for the primer pair of SEQ ID NO: 1 and 2 since these primers consist of wildtype sequences and numerous equivalent primers comprising the known bovine B2AR gene sequences, including SEQ ID NO: 1 and 2, would have been obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the kits of Hughes so as to have included primers to the bovine B2AR gene, and particularly the primers of present SEQ ID NO: 1 and 2, together with the SmaI restriction enzyme, in order to have generated kits that would facilitate the amplification and cloning of bovine B2AR gene sequences, thereby permitting additional analysis of the expression and functional properties of the gene sequences and encoded protein products.

Note that an obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634